Probiotics and prebiotics: microflora management for improved gut health

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A delicate balance exists between the gastrointestinal microbiota and its host animal. It is a symbiotic relationship that has evolved with the host and is essential for optimal health. In the wild state, the equilibrium which is established is seldom threatened. However, under domestic conditions such as those which exist in the human environment, there are several factors, such as diet, medication and stress, which can influence the composition and/or activity of the gut flora—this may often be to the detriment of the host.

At birth, the human intestinal tract is sterile, but it rapidly acquires microorganisms from the mother, other external contacts and the general environment. In developed countries, the baby is born into an environment in which hygiene has a high priority. Consequently, transfer of microorganisms from the mother to offspring may be compromised and the baby could be colonized by inappropriate species of microorganism, such that the characteristic gut flora of the human infant does not fully develop. This is seen in its most extreme form when babies delivered by Caesarean section are transferred to isolators. In these cases, development of the lactobacillus flora is delayed [1]. In a sense, the environment is too clean, but the possibility of transfer of pathogens means that the standards of hygiene cannot be relaxed. Instead, restoration of the gut microflora may be tackled by selectively introducing certain components involved in protection against infection. This has been achieved either by administering live microorganisms (probiotics) or by dosing with chemicals which stimulate the growth and metabolism of bacteria in the lower gut (prebiotics). The formal definitions of these two approaches are as follows:

1. Probiotics are live microbial feed supplements which beneficially affect the host animal by improving its intestinal microbial balance [2].
2. Prebiotics are non-digestible food ingredients that beneficially affect the host by stimulating the growth and/or activity of one or a limited number of bacteria in the colon that can improve host health [3].

Both approaches operate by increasing the number of lactic acid bacteria (e.g. lactobacilli, streptococci, enterococci and bifidobacteria). These groups are normal inhabitants of the gut and have been used in health foods for many years without any adverse effects. Prebiotics target specific bacteria already in the colon. Yeasts (*Saccharomyces cerevisiae* and *Saccharomyces boulardii*) and certain species of *Bacillus* have also been developed as probiotics. Products for human consumption, which exploit both approaches, may have profound effects on certain target groups where the gut flora composition may be compromised. These include infants, the elderly and hospitalized patients. However, it is clear that their development is not directed towards a niche market, but is suitable for the wider approach.

Probiotics

The probiotic approach uses live microorganisms to enhance the microbial population of the lower gut. The minimum effective dose is not precisely known, but numbers in excess of 10^9 CFU/per day are usually recommended. Whether multiplication and colonization of the gut are essential is questionable, because organisms like the yogurt starters (*Lactobacillus delbreuckii* subsp. *bulgaricus* and *Streptococcus salivarius* subsp. *thermo-*

philus), which are often included in probiotic preparations, are not gut colonizers. There is, however, a requirement for survival and active metabolism in order for probiotic effects to be manifested. Therefore, attention to colonization factors such as ability to adhere to the gut epithelial surface may be important to maximize residence time in the gut. Moreover, the most efficacious strains will have enhanced oxygen, pH and bile tolerance.

Although this paper will deal only with the effects that probiotic preparations have on resistance to intestinal infections, it should be noted that claims have also been made for their efficacy in other areas, such as vaginitis, lactose malabsorption, urinary tract infections, cancer and coronary heart disease [4,5].

A great deal of information has accumulated from anecdotal reports and results generated by poorly designed and inadequately analyzed experiments and clinical trials. However, there are good examples of positive results gained from carefully conducted trials in humans, e.g. those using double-blind, placebo-controlled, crossover techniques. One of the most important, and best-documented, areas is that of antibiotic-associated diarrhea (AAD). *Clostridium difficile* is recognized as the causative agent of pseudomembranous colitis, which often follows administration of antibiotics, especially broad-spectrum preparations. The condition can be difficult to resolve by conventional means. Yeast probiotics have given encouraging results. In two well-controlled trials, a large number of patients were treated with *Saccharomyces boulardii*. This treatment resulted in a significant reduction in the number of patients developing AAD [6,7]. The mechanism of effect is still not known but it has been suggested that the yeast may be moderating the effects of *Clostridium difficile* by degrading receptors on the gut wall specific for cell adhesion or toxin binding [8].

Overgrowth of *Candida* in the gut is also a frequent consequence of antibiotic therapy. Studies in hamsters have shown that the gut microflora is involved in suppression of *Candida albicans* [9]. In gnotobiotic mice, *Saccharomyces boulardii* protected against colonization of the gut by *Candida albicans* [10]. One human trial in patients undergoing chemotherapy treatment for leukemia showed that a milk preparation containing *L. acidophilus* and a *Bifidobacterium* species was effective in reducing the count of *Candida* in feces [11].

There is also evidence that *Lactobacillus* GG can influence the course of diarrhea in children. In a well-controlled trial it was shown that administration of this probiotic could reduce the duration of diarrhea in children aged 4–45 months. The results were most pronounced when the data were related to those patients with confirmed rotavirus infection [12].

For probiotics containing bifidobacteria, there have been encouraging results against AAD [13,14], *Clostridium difficile* [15] and childhood forms of diarrhea [16,17].

There is therefore evidence for activity of probiotics against a wide range of intestinal pathogens. Despite this, the mechanisms of effect have been poorly defined. However, it can be speculated that one or more of the following possible effects are in operation:

- competition for nutrients;
- secretion of antimicrobial substances (e.g. bacteriocins, peroxides);
- reduction of gut pH;
- blocking of adhesion sites;
- repression of virulence;
- blocking of toxin receptor sites;
- immune stimulation (local and systemic);
- suppression of toxin production.

Probiotics is a generic term that covers a wide variety of different products comprising tablets, powders, fermented milks (bioyogurts) and liquid suspensions. They may contain from one species of microorganism (e.g. Yakult) to as many as seven (e.g. Protexin). It is, therefore, difficult to summarize all the variable effects that have been reported. Not all trials give positive results; there are many good reasons for this variation, not the least being the low viable counts of some preparations [5]. However, there are many reliable trials which confirm the activity of probiotic preparations and show that gut microflora modulation has the potential to generate significant effects on the health of the consumer.

Prebiotics

The concept of selected microflora modulation by diet is not a new one. However, the term 'prebiotic' was first coined in 1995 to describe dietary components that could influence the composition of the human large gut such that probiotic microorganisms, such as bifidobacteria, could predominate [3]. In operation, prebiotics therefore act like dietary fiber-type carbohydrates in that they enter the colon in an intact form and are fermented by the large gut flora. However, as prebiotics require a selective type of metabolism, they act in a much more specific manner than fibers.

Most present attention is directed towards oligosaccharides, particularly those which contain fructose. A number of human volunteer trials have demonstrated that fructo-oligosaccharides (FOS) are very adept at stimulating bifidobacterial growth in the large intestine [e.g. 18–20]. While the definitive health consequences of prebiotic intake remain to be defined, there is much current interest in influences on pathogenic bacteria,

bowel cancer, cholesterol levels, mineral absorption and gut immune function. In essence, therefore, the targeted health benefits are similar to those of probiotics. Both approaches aim to enhance the activities of 'health-promoting' bacteria.

In terms of product range, it is probable that prebiotics have the wider role. As they exploit non-viable food ingredients, survivability in the product and after ingestion is not a major issue. Moreover, prebiotics should not be affected by heat treatment. In particular, dairy products, infant formula feeds, cereals, weaning foods, drinks, confectionery and biscuits would be appropriate vehicles for use. However, it is important that the minimum dose required be determined. In this respect, it would appear that 4 g/day of FOS exerts a reasonable prebiotic effect. It would be very difficult to attain this level of intake through the consumption of foodstuffs that have a high FOS content (e.g. onions, asparagus, chicory, artichoke, banana). A more feasible route, therefore, appears to be the deliberate incorporation of FOS, and related compounds, into products such as those mentioned above.

Most research on bifidogenic prebiotics has involved FOS and, to a lesser degree, galacto-oligosaccharides (GOS) [21], whilst lactulose has also aroused interest as a good stimulator of lactobacilli in the gut [22]. However, it is almost certain that other prebiotics exist. For example, mannose-, maltose-, xylose- and gluco-oligosaccharides have not been well researched. Moreover, advances in enzyme technology offer the potential for manufacture of 'designer' prebiotics. In some cases, these may have certain advantages over the current market leaders. Some examples of how this may be achieved are as follows:

- lower dosage effects than FOS/GOS;
- enhanced sensory properties;
- more than one biological activity (e.g. prebiotic as well as anti-adhesive);
- stimulate both bifidobacteria and lactobacilli;
- clear repressive effects on known pathogens;
- good viscosity regulation;
- ability to attenuate virulence in pathogens as well as act like prebiotics;
- gastrointestinal, as well as systemic, effects;
- ease of incorporation into common foodstuffs.

The future search for efficacious probiotics and prebiotics should exploit the latest techniques available to bacteriologists and nutritionists. In this case, a molecular approach to gut microbiology is indispensible. It is important that microflora changes in response to dietary intervention are tracked with precision and reliability. Here genetic fingerprinting, probe development, molecular marking and gene-sequencing procedures [23] offer much promise over the conventional phenotypic approach, which is prone to error through metabolic plasticity of the organisms, operator subjectivity and the laborious nature of the analysis. In particular, probing technologies are attractive for use in large-scale volunteer trials, where effects on fecal microorganisms can be detected on stored samples.

Conclusions

The gastrointestinal microflora is an important element in the health of the host animal. Environmental factors, diet, medication and stress can all adversely affect the composition and/or activity of the gut flora. The deficiencies created can be repaired either by added viable organisms (probiotics) or by stimulating specific components (e.g. bifidobacteria) of the flora with chemical supplements (prebiotics). In these two different ways, the gut flora may be reconstituted to allow the host to derive maximum benefit from the association. It is clear that in the development of probiotics and prebiotics, the realistic health consequences must not be lost sight of. This article has suggested that promotion of resistance to gastrointestinal infections offers a great deal of promise. It is important that well-conducted trials are carried out to exploit this simple method of consumer protection.

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